Chronical Chagas Illnes: Controversial aspects about its ethiological treatment.

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Summary
The treatment of Chagas illness in its chronic phase has arised many controversies about its application. In the 80's many investigators began to use those compounds in this phase of the illness, with the justification of controlling an evolutive known process; to be able to erradicate the parasite from the blood and eliminate with this, the human reserves of the parasite designed to interrupt the chain of transmission; diminish the incidence both post transfusional and congenital Chagas and thus preventing the appearance of cardiopaties.
The published studies about the clinical evolution of the illness after the treatment, offer controversial results due to the methods used for the evaluation, the scarce of cases and also for the control of the studies.
Among the serological methods we use the indirect hemaglutination (HAI), indirect inmunofluorescence (TIF) and the Elisa. The diagnosis rules since 1995 already stated the treatment in latent phase till 5 years and according to medical criteria, the convenience of extending till older children.
Those rules were modified in 1998 and stated the treatment in latent phase and adults. We think that scientific reliable information must be produced, though multicentric studies, to put light on dark points and we should revise criteria to evaluate cure; this is a particularly complex situation that creates difficulties in relation to clinical, serological and parasitological aspects. At the same time, we think it is advisable to go on searching new drugs for the treatment of the illness with the requirements of WHO.

Introduction
The population of Argentina is about 33 million of in habitants [1] and shows variables in the prevalence of patients with positive serology, going from 2% to 11% [2-3] according to the (endemicity) of the region.
In high (endemic) region, 6,3 million people [4-5] are exposed to develop a miocardic illness both in its delayed phase and in the phase related to problems of conduction, according to the evolutive way, and influenced by regional factors, immunological state, socio economic conditions and parasite stub.
The infection is characterized for a sharp oligosymptomatic phase, a latent phase or without determined symptoms and a symptomatic chronical phase [6]. If we observe the group of asymptomatic seropositive patients during the evolution that can last decades, about 25 to 30% present symptoms and signs in the level of the central nervous system, digestive system and particularly in the cardiovascular system, a group of patients have a cardiac compromise without clinic manifestations and a 10% present clinic manifestations, due to specific alterations of muscular fibers in the conduction systems, whose symptoms of cardiac insufficiency are associated to a disorder in that particular system.
With the object of controlling Chagas and since 1960 with the creation of the National Chagas program, the following measures were proposed:
a) elimination of the vector insect.
b) chimiotherapy of infected patients with efficient drugs to eliminate human reserves of Tripanosoma Cruzi [7].
c) control of blood banks.
d) control of congenital transmission.

Antecedents of therapy with ethiological drugs
Salvador Mazza began to use the ethiological treatment in 1937 for Chagas illness using Bayer 7602, Bayer 9736 and M 3024 compounds or Cruzon [8]. Since 1965 Nifurtimox [9] was used, with good results in patients coursing the sharp phase of the infection.
Since 1969 many clinical and lab studies showed the effectiveness of tripanomicida of Nifurtimox and Benznidazol drugs during the sharp phase with therapeutic effectiveness till an 80% [10-19]; anyway, they were not considered ideal drugs [10,20-22] due to the appearance of varied secondary effects [23-25] whose most evident manifestations were observed in grown up patients [26-30].

From the 80’s many investigators began to use those compounds in chronical phases of the illness; the reason for its application were:

a) to leave the position of mere spectators in a known evolutive process.
b) to eradicate the parasite from the blood (fundamental for the actions of controlling and eliminating the human reserves of the parasite to interrupt the chain of transmission of the illness).
c) to diminish the incidence both of the post transfusional and congenital Chagas.
d) to prevent the appearance of cardiopathies [31,32].

The demonstration of the presence of the T. Cruzi or its fractions, whose direct action would damage the miocardic level producing chronic miocardiopathy with signs of active inflammatory process, demonstrated by different immunohistochemical and molecular techniques (PCR) [33] has oriented investigators about the need to eliminate the parasite from textures to prevent future lesions [9].

Although the presence of fractions of T. Cruzi in the inner miocardic is given the responsibility of tisular damage through mechanisms of direct action [34], it is also proposed that the productions of alterations [35] by the effect of inflammatory citokinas and reactions or maintained by T cells, with crusade reactivity antimioardic.

Besides, it is possible the participation of anticorps against the themic protein of stress HSP [36].

Based on the mechanisms of miocardic aggression, in 1983 the National Ministry of Health gave the rules for the application of treatment [37], recommending its application only for cases of sharp Chagas, using the two drugs that were available at that moment (Benznidazol and Nifurmitox), including those lactants who are more than 6 months with persistence of positive serologic congenital Chagas. These rules established that the parasitologic, serologic and clinic studies made in chronic patients did not demonstrate the profit of ethiological treatment; for this reason those should not be treated; in the other hand, the frequency of serious colateral effects [18] in some patients receiving this treatment.

During the chronical phase the infected patient treated with the specific tripanomicida drug showed a similar evolution to that of seropositive patients for Chagas illness; that's why, it lacked bases for its application, using as criteria of cure, serologic negativeness which caused different opinions of different authors [38-39].

Romeo Cançado is the one who, in certain way, began the controversy in 1969 when he described the persistence of positive serology in chronical patients treated with tripanomicida, made in controlled studies, applied to that object, parasitological, xeno and serological cure criteria; in this way we see that controversy has been present for a long time [32-40].

Different developed and published studies about the clinic evolution of the illness after treatment with the drugs in use, offer controversial, not very convincing results, particularly due to the methods used for their evaluation, because of few cases shown and also because of the used controls.

In works done by Brazilian and Argentine investigators in chronic patients [24-31], clinic evolution measured in periods of 7 to 8 years did not offer significant differences, related to not treated patients. The appearance of alteration in ECG were very low, thus interpretation of obtained data was difficult, because the comparison between them does not offer significant results.

Before and after the specific treatment of Chagas we recommend rutinary parasitological exams because the reduction of parasitemia or its negativeness suppose to minimize the risk of the evolution to a cardiopathy or rather stop it when it is in course. Some investigators require total disappearance of anticorps as requisite to assure the cure [41-42]. The existence of parasites after the tripanomicida treatment would indicate a failure in this aspect.

Among the serological methods used as cure criteria, the indirect hemaglutination (HAI), the indirect imunofluorescence (TIF) and the immunoenzimatic procedure of ELISA [43], techniques that should be used, because they allow to compare the concentration of anticorps before, during and after the treatment and to be aware of the existence of individual differences in each serological reaction, in relation to the title of the individual samples of serum. Each infected individual reacts in a different way to the existent antigens in the
parasite, both in relation to the affinity of each anticorp and in front of a different number of anticorps [44].

The diagnosis rules, given in 1995 [45] already stated the treatment for children in latent phase and until 5 years, and left to medical criteria the convenience to go until older children. It has to be assumed that the treatment has been barely efficient if in a period from 5 to 10 years of control, there are observed results of negative parasitology with persistence of positive serologic reactions, using tests with conventional serology.

It would be advisable that the design of studies designated to evaluate the therapeutic efficiency includes the practice of serologic reactions with different techniques and with conventional and recombinated antigens, thus allowing the comparison of concentration of initial anticorps with the results during the periodical controls. The determination of high levels of serological titles, states questions that can be related with answers such as:

a) more agresiveness to damage miocardio.

b) persistent presence of parasitemia.

c) more number of parasites.

d) presence of reinfection (in patients in no controlled endemic areas).

Precocious diagnosis and the beginning of specific treatment, in houses under entomologic control can be good signs for better possibilities of obtaining parasitological cure [46].

Sosa Estain’s and de Andrade’s works [31-47] with similar controlled designs, applied a cure criteria based on the negativeness and/or reduction of serology titles and negativeness of Xenodiagnosis. In Sosa Estain’s work [31] there was introduced the use of a recombinating Ag as a marker of serologic cure, gaining in this way a therapeutic efficiency with the BZ from 55 to 62%.

Afterwards, rules from 1983 were modified [37] and in our country new rules were elaborated in June, 1998 [48].

Those rules advise the treatment for:

a) Every patient in the sharp phase of the illness.

b) Children and teen agers in latent phase.

c) Adults in latent phase or incipient or asymptomatic cardiac pathology of the illness.

d) Accidents with contaminated material or with surgeries.

e) Givers or receptors in transplantation of organs.

Hose resolutions were not completely accepted by the investigators, that's why some people accept them with some precautions and only apply the treatment until 12 years old [49]. We understand that the secondary manifestations that the administration of BZ produce, are more important with age, so medication in adults implies a bigger risk, with appearance of phenomena of periferic neuritis, digestive and dermatologic problems (Steven -Johnson), etc.

In those cases, it is necessary to evaluate the relation cost-benefit before applying the treatment.

Points 2 and 3 of that resolution increase controversy, both because of the small number of cases in controlled studies with parasitologic and serologic cure criteria that give sustained evidences of the benefits of tripanomicida therapy (points 2) and the few evidences of the therapeutic efficiency in grown ups with consistent results (points 3). Thus 3 deserves more consideration and debate in scientific institutions and forum, to generate criteria with foundations supporting them.

Brazil adopted a position similar to that of Argentina, recommending treatment of Chagas in sharp, latent and chronic phases, in patients that do not present severe symptons of cardiopaties or digestive problems [50].

Some investigators [51-52-53] suggest treatment in adults in chronic phase, maintaining that it gives the patient the probability of preventing or diminish the incidence of cardiopaties or even stop its evolution, decreasing morbimortality in patients with cardiopaties. It would be necessary to make a difference between 2 kinds of patients: those living in endemic areas (without vectorial controls) and urban patients (migrations to cities in endemic areas) because they need different strategies of treatment. What would happen with a chronic Chagas patient if treated with tripanomicida drugs.

Although the parasite is being erradicated, are we really stopping the autoinmune processes that cause damages in miocardic texture? This is a question that requires answers.
Several authors [49-54-55] do not impulse the application of the treatment in sharp phase patients because of the low possibilities of parasitological and serological cure, with doubtful clinic benefits in the long run and collateral intense effects suffered by patients in sharp phase of the illness living in endemic areas [56]. It is also sustained that the evaluation of the efficiency of the treatment is very complex, as the infection itself [57].

Nowadays the rules of diagnostic and/or therapeutic behaviours are elaborated in function of Medicine Based on Evidences (MBE) [58]; it would be necessary to evaluate according to the knowledges we have, the results related to the application of specific treatment of Chagas during the chronic phase in grown ups.

This question should be answered through the advices of MBE, thanks to definite and indisputable evidences, observed in pathologies like those we now analyze (besides the information we have without definite sustain), to suggest effective therapeutic strategies.

The development of meta-analytical techniques contributes to clarify concepts, and makes it easier the communication of information among professionals with the creation of data base and access to bibliography about recent clinic investigation thanks to Internet, what allows us to take decisions with the base of scientifically demonstrated knowledges.

It is also important to make use of studies containing description of clinic and methodologic aspects about the evolution of morbimortality [59] and the importance of the production of scientific information with sustained evidences, through the making of studies with experimental designs that include the registry of clinic evolution of the illness (cure criteria), testing the traditional agents or maybe some new ones.

Villar J.C. and Col. [60] recently contributed with new meta-analysis techniques, that allow evaluation of effectiveness of different tripanomicida drugs in patients infected by T. Cruzi without evidences of cardiac damage with results of reduction of titles of anticorps and parasitemia, statistically significant for the studied proofs. This analysis was made through the study of registered works on Internet data base. There were included 1306 studies and only 5 of them [31,47,61,62,63] of a number of 756 people had the established conditions for inclusion criteria.

The rest lacked information related to methodologic aspects and omitted clinic aspects of the illness as cure criteria in the evaluation of the clinic efficiency of these agents. It's relevant nowadays with actual knowledges about specific therapy of chronic Chagas, because of the importance given to the evaluation of the clinic results of the different studies related to the efficiency evaluation both in latent and chronic phases of the illness.

Those promoting the application of treatment in chronic phase [64] maintained that the patient has to receive ethiologic treatment with Benznidazol because:
1) If Benznidazol is able to cure the sharp infection.
2) Is able to cure recent chronic illness (children and teen agers) similar to sharp cases.
3) Is able to cure in low percentages the chronic long lasting illness.
4) Has a suppressive effect of parasitemia in the long lasting chronic illness, with a possible favourable evolution.
5) In daily clinic practice, it has to be the professional's option, in front of a 25 years old patient, woman with children that discovered recently her illness with initial cardiopaty.

Conscious of the stated problems that gave origin to the controversies originated in the last years we think, as scientific institution, that it is convenient to remark some aspects of the problem: in the 1st. place, we have to revise the criteria to evaluate cure; this is a particularly complex aspect that offers difficulties in relation to clinic, serologic and parasitological aspects.

The application of these criteria is determined by an uncertainty in the particular phisiopathogeny of the illness, in which factors caused by the presence of the parasite involve enchaigned answers, such as: immune answer, autoimmunity phenomena, inflammatory reaction, deposits of complex antigenics, tisular damage. All of them with their consequent clinic manifestations that appear after long periods of time. The evaluation of these alterations can be the most difficult.

**Serologic criteria:**
In relation to the parasitological cure criteria, "the cure of the patient" establishes as a supposition the elimination of the parasite, not only from the blood but also from the textures, fact that can't be confirmed in human beings. The parasitological methods (Xenodiagnosis) in chronic phase of the illness, just provide a sensitiveness of about 50%, similar to the hemoculture method.
The use of molecular biology methods (PCR) is seen as an ideal tool to measure parasitemia, specially in patients in chronic phase; anyway, the obtained results and the high costs, do not allow its systematic application.

The use of complementary methods has to exceed the traditional ECG and Rx, to use different methods designated to evaluate disorders of rhythm and registers of continuous ECG (Holter 24 hours of 3 channels), the variation of cardiac frequency (VFC) and the Late Ventricular Potential (PTV), and the morphological and functional systolic and diastolic evaluation of the left ventricle by means of studies with Cardiac Ecodoppler, elements that allow us to check patients before, during and after treatment. It seems to be important to add studies that observe the digestive function, and tests that allow the observation of SNA.

It's important to remark aspects that must be considered before stating treatment in infected patients in chronic phase, such as to be sure that the patient is not living in endemic areas, and if he is, to maintain the house under entomologic control. It is also important to consider age, due in particular to the toxics of available drugs, with secondary effects which are more frequent in grown up patients; as we have already established, these effects increase proportionally with age.

The characteristics of complications can become severe (hepatopaties-Steve-Johnson) and last even after the end of treatment; it is also important the previous evaluation of the patient’s health and be sure that periodical controls will be possible during the treatment.

All these methods or tests allow us to define clearly the basal profile of the patient with the object of judging in the future, through studies, the appearance of indicators revealing the beginning of pathology. We consider important to debate this problem to try to reach to scientific conclusions. The Chagas Committee has organized multicentric national studies to try to answer questions that Chagas states through the elaboration of planned studies following the rules that the scientific method establishes, to produce valid and reliable information.

Among the registries proposed by Chagas Committee and presented in its Internet site, appear:
“Therapeutic Efficiency with Benznidazol in the Latent Phase of Chagas Illness”, whose objectives are [65]:

GENERAL

1. To evaluate the efficiency of treatment with Benznidazol through the use of different cure criteria and parameters of morbility in young people in latent phase of Chagas.
2. To evaluate tolerance and collateral effects.
3. To diminish parasite offer in patients living in urban and rural areas (human reserves of T. Cruzi).

PARTICULAR

1. Criteria of parasitological cure (hemocultures, Xenodiagnosis, PCR).
2. Criteria of serological cure: (HAI-TIF-ELISA with antigens of 1st. and 3rd. generation).
3. Parameters of clinic morbility.
   1) ECG in quietness state.
   2) Thoracic Rx.
   3) Ecocardiography.
   4) Cardiac Doppler.
   5) ECG ambulatory 24hs.
   6) Late ventricular potentials.
   7) Variation of cardiac frequency.

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   It has been planned with non controlled designs because it had to be taken into consideration by the Bioethic Committee, as there are national rules that indicate the use in children and grown ups, and we weren’t able to find scientific works to refuse them. This study with periodical controls during 4 years uses as cure criteria the following parameters: parasitologic, serologic and clinic, as an evidence to value the evolution of the illness with the recommendations of MBE.

Anticipating to the meta analysis results [60] the registry of relative study about the efficiency proposed by the Chagas Committee (actually standing in the Chagas Center and Regional Pathology “Dr. Humberto Lugones”. Santiago del Estero, with 90 patients) states variables of observation that will serve to evaluate aspects of the
clinic evolution of the illness.

We conclude that we have to produce reliable scientific information through multicentric studies to put light in many dark points of the subject to offer new rules clearly based. It is important to go on searching new drugs for the treatment of the illness with the requirements stated by WHO [66] - Meeting of the development of tripanomicida compounds for the sterilization of blood - UNDP/WB/TDR-Geneve) to define an ideal drug that allows: to obtain the parasitological cure in sharp and chronic cases, to obtain effectiveness in one or several doses, to be accessible for patients because of its low cost, do not present colateral or teratogenic effects, do not need hospitalization for its treatment and do not induce resistance.

Multicentric works are available from July 2002 in FAC Web and were well received during their presentation in the XX Chagas Symposium, Cardiology National Congress 2001 and during the Continuous Education Forum.

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